CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, with sufficient postage, in an envelope addressed to: Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on the below date:

Date: March 16, 2006 Name: Steven P. Shurtz Signature: /Steven P. Shurtz/

BRINKS HOFER GILSON &LIONE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Appln. of: Robert J. Yatka et al.

Appln. No.: 10/712,114 Examiner: Arthur L. Corbin

Filed: November 13, 2003 Art Unit: 1761

For: METHOD OF CONTROLLING RELEASE OF N-SUBSTITUTED DERIVATIVES OF ASPARTAME IN CHEWING GUM AND GUM PRODUCED THEREBY

Attorney Docket No: 1391/1561

Mail Stop Amendment
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL

Sir:

Attached is/are:

☒ Appeal Brief with Evidence Appendices A, B and C

☒ Return Receipt Postcard

Fee calculation:

☐ No additional fee is required.

☐ An extension fee in an amount of $_____ for a _____-month extension of time under 37 C.F.R. § 1.136(a).

☒ A petition or processing fee in an amount of $500 under 37 CFR 41.20(b)(2)

☐ An additional filing fee has been calculated as shown below:

						Small Entity			Not a Small Entity	
	Claims Remaining After Amendment		Highest No. Previously Paid For	Present Extra		Rate	Add'l Fee	or	Rate	Add'l Fee
Total		Minus				x $25=			x $50=	
Indep.		Minus				x 100=			x $200=	
First Presentation of Multiple Dep. Claim						+$180=			+ $360=	
						Total	$		Total	$

Fee payment:

☐ A check in the amount of $_____ is enclosed.

☐ Please charge Deposit Account No. 23-1925 in the amount of $. A copy of this Transmittal is enclosed for this purpose.

☒ Payment by credit card in the amount of $500.00 (Form PTO-2038 is attached).

☒ The Director is hereby authorized to charge payment of any additional filing fees required under 37 CFR § 1.16 and any patent application processing fees under 37 CFR § 1.17 associated with this paper (including any extension fee required to ensure that this paper is timely filed), or to credit any overpayment, to Deposit Account No. 23-1925.

Respectfully submitted,

March 16, 2006
Date

/Steven P. Shurtz/
Steven P. Shurtz (Reg. No. 31,424)

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope, with sufficient postage, addressed to: Commissioner for Patents, Post Office Box 1450, Alexandria, VA 22313, on

March 16, 2006
Date of Deposit

Steven P. Shurtz, Reg. No. 31,424
Name of Applicant, Assignee or Registered Representative

/Steven P. Shurtz/
Signature
March 16, 2006
Date of Signature

Our Case No.: 1391/1561

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: ROBERT J. YATKA et al.

Serial No.: 10/712,114 | Examiner: Arthur L. Corbin

Filing Date: November 13, 2003 | Group Art Unit No.: 1761

For: METHOD OF CONTROLLING RELEASE OF N-SUBSTITUTED DERIVATIVES OF ASPARTAME IN CHEWING GUM AND GUM PRODUCED THEREBY

APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This is an appeal from the Final Rejection dated November 3, 2005, of claims 6, 11, 24-27, 30 and 31, all the rejected claims pending in the above captioned case.

I. REAL PARTY IN INTEREST

The present application is owned by the Wm. Wrigley Jr. Company.

II. RELATED APPEALS AND INTERFERENCES

There are no related Appeals or Interferences for this case. This case was previously appealed and an appeal brief mailed May 23, 2005. However, after receiving the appeal brief, the Examiner reopened prosecution, which continued until a new Notice of Appeal was filed.

This case is a continuation of U.S. Patent Application Serial No. 09/731,036, filed December 5, 2000, (now U.S. Patent No. 6,692,778), which in turn is a continuation of PCT Application Serial No. PCT/US98/11741, filed June 5, 1998.

III. STATUS OF CLAIMS

Claims 6, 11, 24-27, 30 and 31 are pending. Claims 1-5, 7-10, 12-23 and 28-29 were previously cancelled. Claims 6, 11, 24-27 and 30-31 were all rejected, and are all being appealed. No claims have been allowed. Claims 32 and 33 in the Amendment mailed February 3, 2006 have not been entered (see below).

IV. STATUS OF AMENDMENTS

An advisory action mailed February 14, 2006 noted that the Amendment mailed February 3, 2006 after the Final Rejection would not be entered because it was not deemed to place the application in better form for appeal and because it presented additional claims without canceling a corresponding number of finally rejected claims.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention relates to producing chewing gum products containing N-substituted derivatives of aspartame. The application discloses various ways of treating the N-substituted derivatives of aspartame to control their release and enhance shelf-life stability. U.S. Patent No. 6,692,778, the patent resulting from the parent of the present application, covers a number of ways of treating the N-substituted derivatives of aspartame. The claims in the present application are directed to two additional treatment methods.

In recent years, efforts have been devoted to controlling release characteristics of various ingredients, such as sweeteners and flavors, in various chewing gum

formulations, to thereby lengthen the satisfactory chewing time of the gum and avoid an undesirable overpowering burst of sweetness or flavor during the initial chewing period. In addition, other efforts have been directed at perfecting the use of high-potency sweeteners within the chewing gum formulation, to thereby increase the shelf-life stability of the ingredients, *i.e.* the protection against degradation of the high-potency sweetener over time. Specification, page 1, lines 14-25

A recently identified class of high-potency sweeteners are N-substituted derivatives of aspartame. Some of these sweeteners may give a long lasting sweetness release when used in chewing gum, while others may give a fast release that may not be compatible with the release of flavor. By modifying N-substituted derivatives of aspartame by various methods, a controlled release from chewing gum can be more effective to balance sweetness with flavor and give a highly consumer acceptable product. The class of N-substituted derivatives of aspartame useful in the present invention are described in U.S. Patent No. 5,480,668. One particularly preferred N-substituted derivative of aspartame is commonly known as neotame. The chemical name of this sweetener is N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester. Other preferred N-substituted derivatives of aspartame sweeteners include two other similar chemicals, namely N-[N-[3-(4-hydroxy-3-menthoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester and N-[N-(3-phenylpropyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester. Specification, page 1, line 26 to page 2, line 15.

While neotame was suggested for use in chewing gum in the prior art, there was no indication of how the sweetener might release from the chewing gum, and whether its release rate could or should be modified. However, the present inventors speculated that neotame would release slowly from chewing gum during the early stages of mastication of the gum because of its low solubility in water. Therefore, it would be a significant improvement to a chewing gum to have neotame sweetener release its sweetness more quickly along with some of the flavor in the gum, thus balancing the overall taste perception. Specification, page 5, lines 4-11

The present inventors developed methods of controlling the release of N-substituted derivatives of aspartame. Previously mentioned U.S. Patent No.

6,692,778 covers methods of controlling release involving physical modifications of the sweetener by encapsulation with another substrate, such as spray drying, spray chilling, fluid-bed coating and coacervation. These encapsulation techniques that give partial encapsulation or full encapsulation can be used individually or in any combination in a single step process or multiple step process. Generally, delayed release of sweetener is obtained in multistep processes like spray drying the sweetener and then fluid-bed coating of the resultant powder. Specification, page 6, lines 18-28.

Another method of isolating the N-substituted derivative of aspartame from other chewing gum ingredients is to add the sweetener to the dusting compound of a chewing gum. A rolling or dusting compound is applied to the surface of chewing gum as it is formed. This rolling or dusting compound serves to reduce sticking to machinery as it is formed, reduces sticking of the product to machinery as it is wrapped, and sticking to its wrapper after it is wrapped and being stored. The rolling compound comprises a N-substituted derivative of aspartame in combination with, preferably, mannitol, sorbitol, sucrose, starch, calcium carbonate, talc, other orally acceptable substances or a combination thereof. The rolling compound preferably constitutes from about 0.25% to about 10.0%, more preferably about 1% to about 3% of weight of the chewing gum composition. The amount of N-substituted derivative of aspartame added to the rolling compound is preferably about 0.001% to about 1% of the rolling compound or about 0.1 ppm to about 100 ppm of the chewing gum composition. Specification, page 11, lines 6-19.

Another method of isolating the N-substituted derivative of aspartame is to use it in the coating/panning of a pellet chewing gum. Pellet or ball gum is prepared as conventional chewing gum, but formed into pellets that are pillow shaped, or into balls. The pellets/balls can then be sugar coated or panned by conventional panning techniques to make a unique sugar coated pellet gum. The N-substituted derivative of aspartame is very stable and slightly water soluble, and can be easily added to a hot sugar solution prepared for sugar panning. The N-substituted derivative of aspartame can also be added as a powder blended with other powders often used in some types of conventional panning procedures. Levels of use of the N-substituted derivative of aspartame may preferably be about 2 ppm to about 500 ppm in the coating and about 1

ppm to about 200 ppm of the weight of the chewing gum product. The weight of the coating may preferably be about 20% to about 50% of the weight of the finished gum product. Specification, page 11, line 24 to page 12, line 6.

Thus, in a first aspect, the invention includes a method of producing a chewing gum product containing a N-substituted derivative of aspartame wherein the N-substituted derivative of aspartame is applied as a part of a rolling compound applied on the chewing gum product. See claim 24.

In a second aspect, the invention includes a method of producing a chewing gum product containing an N-substituted derivative of aspartame wherein the N-substituted derivative of aspartame is applied as a part of a coating on a chewing gum pellet, the coating being formed by a panning procedure. See claim 26.

These methods of using neotame sweetener in the chewing gum can allow a lower usage level of the sweetener, can give the sweetener a more controlled release rate, and can reduce or eliminate any possible reaction of the sweetener with gum base, flavor components, or other components, yielding improved shelf stability. Specification, page 11, lines 19-24, and page 11, line 32 to page 12, line 2.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Claims 6, 11, 24-27 and 30-31 were rejected under 35 U.S.C. § 103(a) as unpatentable over U. S. Patent No. 5,480,668 (Nofre '668) in view of U.S. Patent No. 4,997,659 (Yatka).
2. Claims 6, 11, 24-27, 30 and 31 were rejected under 35 U.S.C. §103(a) as unpatentable over U. S. Patent No. 5,510,508 (Nofre '508) or Nofre '668 in view of U.S. Patent No. 4,374,858 (Glass) and Yatka.

VII. ARGUMENT

A. Claims 6, 11, 24-27 and 30-31 are patentable over U. S. Patent No. 5,480,668 (Nofre '668) in view of U.S. Patent No. 4,997,659 (Yatka).

Claims 6, 11, 24-27, 30 and 31 were rejected in the Final Rejection under 35 U.S.C. §103(a) as unpatentable over U. S. Patent No. 5,480,668 (Nofre '668) in view of U.S. Patent No. 4,997,659 (Yatka). This rejection is improper and must be reversed.

Claims 6, 24-25 and 30 require using an N-substituted derivative of aspartame as part of a rolling compound on a chewing gum product. Claims 11, 26-27 and 31 require using an N-substituted derivative of aspartame as part of a coating formed by panning a chewing gum pellet. While Nofre '668 discloses the N-substituted derivatives of aspartame used in the present invention, Nofre makes no suggestion for using the disclosed sweeteners in a rolling compound for chewing gum or in a panned chewing gum coating.

Yatka, on the other hand, discloses different ways of using a completely different sweetener, alitame, in chewing gum. While Yatka discloses using alitame as a part of a rolling compound and in a pellet coating, there is no suggestion in Yatka to use other sweeteners in this fashion. There is no reason from the references themselves to combine the references and use N-substituted derivatives of aspartame the way alitame was used in Yatka. This rejection is thus based on hindsight.

Just because one high-potency sweetener was used in a particular fashion in producing chewing gum does not mean that it would have been obvious to use other high-potency sweeteners in the same fashion. Moreover, alitame was suggested for use in these ways in Yatka because of a desire to delay its release or separate it from other ingredients which may cause the alitame to degrade. The need for delayed release or prevention of degradation has not been shown in the prior art as being applicable to N-substituted derivatives of aspartame. Rather, Nofre '668 shows the stability of the N-substituted derivatives of aspartame disclosed therein when used in chewing gum (see col. 3, lines 51-60); and there is no suggestion that the materials release too quickly from chewing gum.

The Final Rejection notes that Nofre teaches to mix a N-substituted derivative of aspartame with alitame and then add that mixture into chewing gum. The Final Rejection then goes on to argue that it would have been obvious to use this mixture in place of the pure alitame in the way that Yatka teaches to use alitame by itself. This argument is also based on hindsight. The most that a person of ordinary skill in the art would learn from Nofre is to add the mixture to edible products, not even chewing gum specifically. Again, there is no teaching in Nofre to use the mixture in other ways, such as in a rolling compound or in a panned coating, or to use it in place of alitame in other

ways that alitame is used. Nor is there anything in Yatka that teaches to use combinations of sweeteners in place of alitame. There is nothing in Yatka that would suggest treating a combination of alitame and an N-substituted derivative of aspartame the same way that alitame was used, and nothing in Nofre that would suggest looking at Yatka for ideas about how to include mixtures of alitame and an N-substituted derivative of aspartame in chewing gum products. While Yatka teaches to use alitame in a chewing gum coating or in a rolling compound, it does not suggest that any other high-potency sweetener should be mixed with the alitame and used in the same way. The simple fact of the matter is that the combination suggested by the Final Rejection in making the rejection would not have been made without hindsight of the present invention.

In order for a *prima facie* case of obviousness to be established, the teachings from the prior art itself must suggest the claimed subject matter to one of ordinary skill in the art. The mere fact that the prior art could be modified as proposed in the Final Rejection is not sufficient to establish a *prima facie* case of obviousness. The Final Rejection must explain why the prior art would have suggested to one of ordinary skill in the art the desirability of the modification. *See In re Fritch*, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1783-84 (Fed. Cir. 1992). The Final Rejection gives no reason to make such a combination. The rejection is thus based on impermissible hindsight reconstruction of the invention.

The Final Rejection takes the position that alitame is a well known sweetener, and the ways alitame are used in Yatka would make it obvious to apply the teachings of Yatka to "other conventional chewing gum sweeteners." Later, the Final Rejection implies that alitame and neotame are "different but similar" sweeteners. At the time of the present invention, neotame could not be considered to be a conventional chewing gum sweetener. While its use in chewing gum is suggested by Nofre '508, that does not make it a conventional sweetener. Neotame was not even approved for use as a sweetener in food in the U.S until July, 2002 (see page NCB of brochure titled "New Approaches to the Product Developer's Dilemma" from the NutraSweet Company, four pages, attached hereto as Appendix A) (hereinafter referred to as "Neotame Brochure"), which was well after the 1998 effective filing date for the present application. Also,

neotame has quite distinct properties compared to alitame. While neotame has a water solubility of at 25°C of 1.3% (Neotame Brochure, page NCD), alitame has a water solubility 10 times greater, 13.1% (see fourth page of collection of pages from Pfizer brochure on Aclame (its trade name for alitame), attached hereto as Appendix B). This difference in solubility is one of the reasons alitame release from chewing gum much more quickly than neotame. Further, since neotame has a dimethlybutyl addition to its chemical structure, it is lipophilic, and thus it becomes more easily bound to the gum base, again making it release more slowly from chewing gum than alitame.

At the bottom of page 3, the Final Rejection also takes the position that Nofre '668 does not support Applicants' position that N-substituted derivatives of aspartame are more stable in chewing gum than aspartame. However, Nofre '668 col. 3, lines 51-60 teaches that N-substituted derivatives of aspartame are more stable than aspartame under the common conditions of use for food preparations, and notes that the N-substituted derivatives will be better than aspartame for stability in foods that have a pH around 7, such as chewing gum.

The first full paragraph on page 3 of the Final Rejection includes some statements that are incorrect. Applicants did not conclude that applying alitame to chewing gum in a panning procedure will delay its release. In fact, they believe it will increase its release. Rather, Applicants remarks point out that Yatka teaches applying alitame in a gum coating to separate it from other gum ingredients, to thereby improve its stability. Second, the third sentence refers to using a panning procedure to apply a sweetener to chewing gum as part of a rolling compound. However, panning procedures are used to produce shell coatings on gum pellets, not apply rolling compounds. Rolling compounds are used as dusting agents during processing of stick and tab gum products.

Since the rejection is based on impermissible hindsight, claims 24 and 26, and claims 6,11, 25, 27 and 30-13 dependent thereon, are patentable over Nofre '668 and Yatka, and the rejection must be reversed.

B. Claims 6, 11, 24-27 and 30-31 are patentable over U. S. Patent No. 5,510,508 and Nofre '668 in view of U.S. Patent No. 4,374,858 (Glass) and Yatka.

In the Final Rejection, claims 6, 11, 24-27, 30 and 31 were rejected under 35 U.S.C. §103(a) as unpatentable over U. S. Patent No. 5,510,508 (referred to on the face of the patent as Claude et al., but referred to in the Office Action as Nofre et al. 5,510,508, and referred to herein as Nofre '508) or Nofre '668 in view of U.S. Patent No. 4,374,858 (Glass) and Yatka. This rejection is also improper and must also be reversed.

Nofre '508 discloses methods of preparing a particular N-substituted derivative of aspartame, but the same material is disclosed in Nofre '668. Nofre '508 also suggests that the compound can be used in chewing gum, but so does Nofre '668. There is no suggestion in Nofre '508 of using the particular N-substituted derivative of aspartame in a rolling compound or panned coating on a chewing gum pellet. Thus Nofre '508 is considered to be cumulative to Nofre '668.

Glass discloses an aspartame sweetened chewing gum, including the use of aspartame in a rolling compound. Col. 4, lines 16-38 outline a test that was conducted to show that aspartame used in this fashion was more stable than aspartame mixed into a chewing gum composition. However, there is no suggestion of using other high-intensity sweeteners in the same fashion, and no suggestion of using N-substituted derivatives of aspartame in this manner.

Just as with the rejection based on Nofre '668 in view of Yatka, there is no explanation in the Office Action of any motivation for combining the references. There in no suggestion in Nofre '668, Nofre '508, Glass or Yatka of using a sweetener used in the way disclosed in one reference the same way that sweeteners used in another reference are used. It is only by hindsight of the present invention that one would consider combining these references. Further, since Nofre '668 teaches that N-substituted derivatives of aspartame are stable in chewing gum compared to aspartame, there would be a no reason from Nofre '668 to use N-substituted derivatives in a manner that aspartame was used in Glass to increase its stability.

The second paragraph on page 4 of the Final Rejection states that "aspartame is quite similar in its properties to applicant's claimed N-substituted aspartame". This

position is traversed. First, it is clarified that claims 24 and 26 call for N-substituted derivatives of aspartame, not N-substituted aspartame. Next, it is noted that neotame, the specific N-substituted derivative listed in claims 30 and 31, is significantly different than aspartame. Neotame is 30-60 times sweeter than aspartame, and is thus used in food at considerably lower concentrations. (See *Neotame: The Next-Generation Sweetener, Food Technology*, vol. 56, No. 7, (July 2002) p.37, attached hereto as Appendix C) (hereinafter referred to as "*Food Technology*"). While its solubility in water is similar to that of aspartame, neotame's lipophilic properties make it more readily soluble in some solvents typically used in food systems. *Food Technology,* p.37. Thus, neotame, and the other N-substituted derivatives of aspartame referred to in Applicants' claims, are not "quite similar" to aspartame. While it is true that they are chemically similar, their properties are quite different, especially in regard to those properties that are important to their use in chewing gum, such as how they interact with gum base and the level at which they are used. Thus, claims 24 and 26, and the claims dependent thereon, are patentable over the cited references, and the rejection must be reversed.

VIII. CONCLUSION

Appellants have made a novel and nonobvious contribution to the art of controlling the release of N-substituted derivatives of aspartame from chewing gum products. The claims at issue distinguish over the cited references. The present invention is not obvious in view the cited prior art. The references are being combined based solely on hindsight reconstruction of the invention. A person of ordinary skill in the art would not combine the references as suggested in the Final Rejection.

Appellants submit that the present invention is fully patentable over the cited references and the Examiner should be REVERSED.

Respectfully submitted,

/Steven P. Shurtz/

Steven P. Shurtz
Registration No. 31,424
Attorney for Appellants

Dated: March 16, 2006

BRINKS HOFER GILSON & LIONE
P.O. Box 10395
Chicago, IL 60610
(312) 321-4200
Direct Dial: (801) 444-3933

CLAIMS APPENDIX

CLAIMS ON APPEAL

6. The method of Claim 24 wherein an additional high-potency sweetener selected from the group consisting of aspartame, alitame, salts of acesulfame, cyclamate and its salts, saccharin and its salts, sucralose, thaumatin, monellin, dihydrochalcone, glycyrrhizin, stevioside and combinations thereof is mixed with the N-substituted derivative of aspartame before it is applied in the rolling compound.

11. The method of Claim 26 wherein an additional high-potency sweetener selected from the group consisting of aspartame, alitame, salts of acesulfame, cyclamate and its salts, saccharin and its salts, sucralose, thaumatin, monellin, dihydrochalcone, glycyrrhizin, stevioside, and combinations thereof is mixed with the N-substituted derivative of aspartame in the coating.

24. A method of producing a chewing gum product containing a N-substituted derivative of aspartame wherein the N-substituted derivative of aspartame is applied as a part of a rolling compound applied on the chewing gum product.

25. The method of Claim 24 wherein the N-substituted derivative of aspartame is selected from the group consisting of:

a) N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester;

b) N-[N-[3-(4-hydroxy-3-menthoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester; and

c) N-[N-(3-phenylpropyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester.

26. A method of producing a chewing gum product containing a N-substituted derivative of aspartame wherein the N-substituted derivative of aspartame is applied as a part of a coating on a chewing gum pellet, the coating being formed by a panning procedure.

27. The method of Claim 26 wherein the N-substituted derivative of aspartame is selected from the group consisting of:

a) N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester;

b) N-[N-[3-(4-hydroxy-3-menthoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester; and

c) N-[N-(3-phenylpropyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester.

30. The method of claim 24 wherein the N-substituted derivative of aspartame comprises N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester.

31. The method of claim 26 wherein the N-substituted derivative of aspartame comprises N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester.

EVIDENCE APPENDIX

Brochure titled "New Approaches to the Product Developer's Dilemma" from the NutraSweet Company, four pages, attached hereto as Appendix A

Collection of pages from Pfizer brochure on Aclame (its trade name for alitame), attached hereto as Appendix B

Neotame: The Next-Generation Sweetener, Food Technology, vol. 56, No. 7, (July 2002) pp. 36-45, attached hereto as Appendix C

RELATED PROCEEDINGS APPENDIX

None

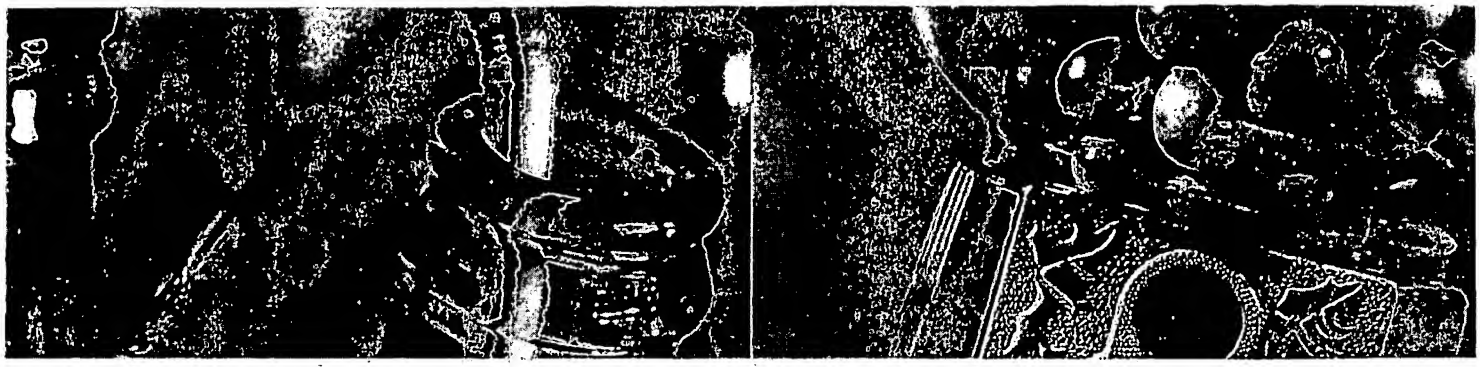
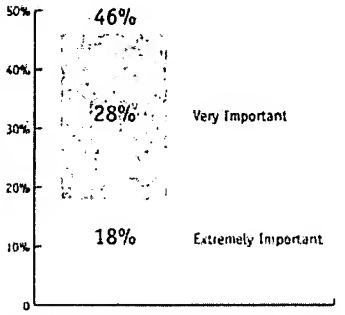


figure 1 | Less Sugar

Importance of sugar reduction to improving overall health.



Source: The NutraSweet Company Consumer Survey (2003). 100 respondents

Consumers want to reduce their sugar intake...

The statistics speak volumes. Consumer anxiety about sugar has doubled in three years, and is now the #2 consumer diet concern, sandwiched between fat (#1) and calories (#3).

A recent consumer study by The NutraSweet Company reports that 46% of all carbonated soft drink users believe that it is "extremely" or "very important" for them to reduce their sugar intake to improve their overall health. *(See figure 1)*

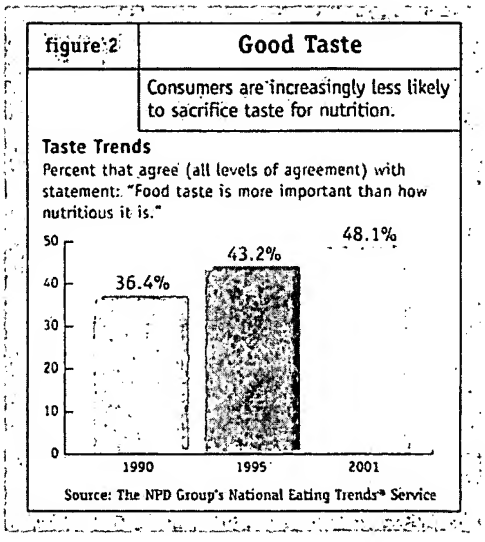
New Approaches to the Product Developer's Dilemma

... But are not willing to sacrifice taste

At the same time, market research data has also shown increasingly that people will not sacrifice great taste for nutritional benefits: A multi-year study by The NPD Group showed that the percentage of consumers who will select a food product's taste over its nutritional benefits has increased from 36.4% in 1990 to 48.1% in 2001. *(See figure 2)*

figure 2 | Good Taste

Consumers are increasingly less likely to sacrifice taste for nutrition.



Alternatives to "diet"

The beverage industry has responded well to growing consumer dietary concerns by introducing a wide array of diet products with no sugar or calories.

However, while diet products meet the sugar and calorie reduction needs of many people, there is a significant segment of consumers who want to reduce their sugar intake for whom there is no ready alternative.

"Our consumer research suggests that most diet beverage drinkers are very satisfied with their diet beverage choices," says Craig Petray, President of The NutraSweet Company. "What is striking, however, is the number of regular beverage users who are highly interested in reducing their sugar intake but strongly prefer the taste of regular versus diet beverages. The current beverage market doesn't offer these consumers many alternatives."

A new solution

In July 2002, the U.S. Food and Drug Administration approved neotame, a new sweetener specifically designed to reduce sugar while providing all the flavor of a regular beverage. Developed by The NutraSweet Company, neotame offers product developers significant advantages for reducing sugar in beverage, confectionery and food products.

Questions & Answers About Neotame

What is neotame?

Neotame is a new sweetener and flavor enhancer, that has a clean sweet taste like sugar. *(See figure 3)* Because it is so intensely sweet (about 7000-13000 times sweeter than sugar), only very small amounts are needed to sweeten foods and beverages.

Who can consume neotame?

Everyone including children, pregnant and breastfeeding women, and people with diabetes can use neotame as a sweetener and flavor enhancer.

What are the key benefits of neotame?

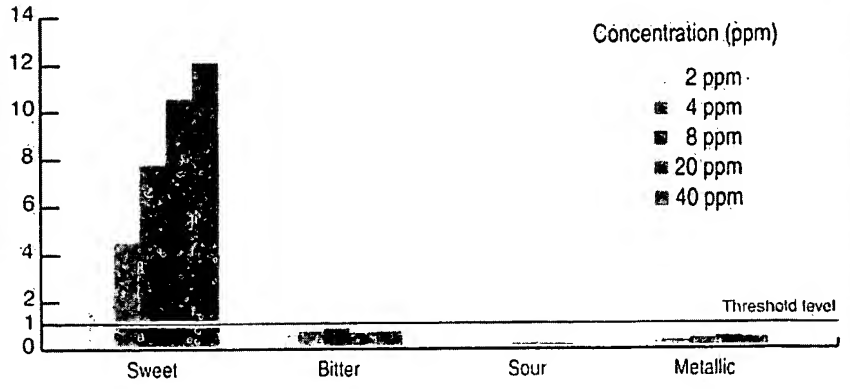
Neotame provides food and beverage manufacturers with greater flexibility and value in delivering food and beverage products that meet consumers' expectations regarding health and taste.

Neotame can be blended with nutritive sweeteners, including high fructose corn syrup and sucrose, as well as with other high-intensity sweeteners, to match the taste of existing products or to develop new or improved tasting products. Neotame is a versatile food ingredient and is compatible with other food ingredients. Efficacy and potency will vary depending upon the actual application in which neotame is used.

figure 3

Neotame Descriptive Taste Profile in Water

Neotame has a clean taste with no bitter or metalic notes — as concentration increases, only sweetness increases.



Source: Duke trained panel (ss#3061) June 1998

• As a ***sweetener***, neotame can replace a portion of the sweetness and calories from nutritive sweeteners without compromising taste. *(See figure 4)*

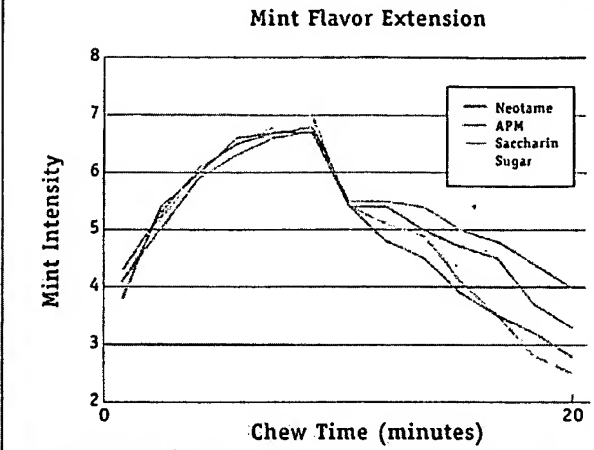
As a ***flavor enhancer***, neotame can be used to create improved taste and flavor in a variety of food and beverage products at sweetening or sub-sweetening levels. In certain applications and flavor systems, neotame extends and enhances taste and flavor. For example, after chewing mint-flavored chewing gum for 20 minutes, sensory panelists reported that neotame-sweetened chewing gum had more mint flavor than samples sweetened with other sweeteners, including sugar. *(See figure 5)*

Neotame has been shown to modify and mask off-flavors when used at sweetening levels. Therefore application may include:

— Masking of off notes, e.g. vitamin and mineral fortification or other notes such as soy flavor
— Increased perception of flavor over an extended period
— Rounding out of flavor notes

figure 5 **Neotame Flavor Enhancement**

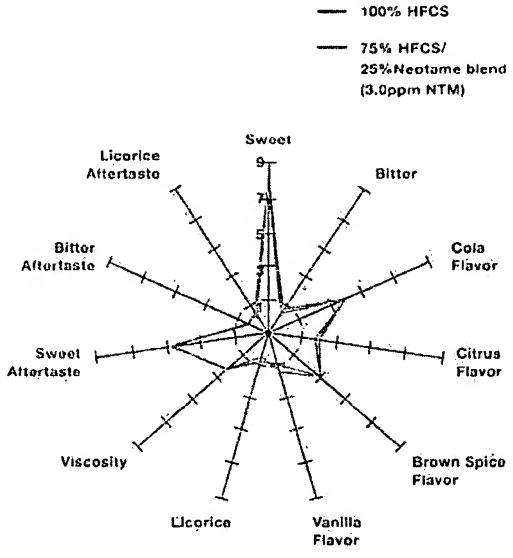
Neotame's influence on peppermint flavor in chewing gum.



Source: ML Prospect trained panel,
8 samples evaluated in duplicate October/November, 1999

figure 4 **Neotame Flavor Profile**

Descriptive taste profile of a neotame (NTM)/high fructose corn syrup (HFCS) blend in cola-flavored carbonated soft drink.



(Source: Study SS#3542 on file at The NutraSweet Company)

• ***Cost reduction*** is a key benefit of using neotame. Its low cost and high potency combine to make it one of the lowest cost sources of sweeteness available to formulators. Use of neotame as a sweetener source in either traditional or sugar-free food and beverages offers dramatic reductions in overall sweetener costs.

The low usage levels for neotame create the opportunity to deliver improved value throughout the supply chain. For example, the sweetness equivalency of eight metric tons of sugar can be replaced with as little as 1 kg of neotame reducing storage and shipping charges.

Use of neotame can also allow for reduction in other costly components such as acid and flavor in some applications because of its flavor enhancing ability.

• Neotame provides ***consumer friendly labeling***. Neotame is safe for everyone, contributes no calories and does not require special labeling for phenylketonuric individuals.

figure 6	Neotame Product Overview
	Neotame product specifications
Identification test	Conforms to standard
Assay (dried basis)	97.0% to 102.0%
Moisture	< 5.0%
Residue on ignition	<0.2%
Specific rotation $[\alpha]_D^{20°}$	40.0 to 43.4°
Other related substances	< 2.0%
N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine	<1.5%
Lead	<1 mg/kg
	Neotame physical description
Color	White to off white
Form	Powder
Molecular Formula	$C_{20}H_{30}N_2O_5$
Molecular Weight	378.47
pH (0.5% solution)	5.0 to 7.0
Solubility at 25° C	>100g per 100g of ethanol
	~1.3g per 100g of water
Taste	Sweet

How is Neotame Different From Other Sweeteners?

Neotame offers formulators a unique tool when developing a wide variety of products. Neotame delivers a clean sweet taste without any significant off-notes. Furthermore, as neotame concentration is increased, only sweetness increases. This eliminates the occurrence of off-notes associated with diet or sugar-free products.

In what products can neotame be used?

Neotame can be used in

- Beverages
- Tabletop sweeteners
- Chewing gums and confectionery
- Baked goods
- Frozen desserts, ice cream, yogurt
- Cereals

Neotame also has application in pharmaceutical products and nutritional supplements and many other applications.

In which countries is neotame available?

As of August 2003, neotame is available in the following countries:

- U.S.
- ***Latin America***: Costa Rica, Ecuador, Guatemala, Mexico, Peru and Trinidad & Tobago
- ***Europe/Mid East***: Bulgaria, Czech Republic, Iran, Poland, Romaina, Russia and Slovakia
- ***Asia/Pacific***: Australia, China, New Zealand and Philippines

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) favorably reviewed neotame in June 2003.

Neotame Product Specifications

(See Figure 6)

Ingredients

Neotame: N-[N-(3,3-dimethylbutyl)-L-α- aspartyl]-L-phenylalanine 1-methyl ester is a derivative of the dipeptide composed of the amino acids, aspartic acid and phenylalanine.

Kosher status

The Orthodox Union (OU) certifies neotame as kosher and pareve.

Regulatory status and labeling

Neotame is approved for use as a sweetener and flavor enhancer in foods and beverages. Labeling requirements will vary by country. Contact your NutraSweet representative for more details. Neotame does not need special labeling for phenylketonuric individuals.

Recommended storage

As a dry ingredient, neotame is stable for at least five years at ambient storage conditions, typically 59° to 86° F (15° to 30° C) and 35% to 60% relative humidity, when the inner bags are sealed. Like most dry ingredients, neotame should be stored to avoid high heat and humidity and with the inner bags sealed until ready to use.

Packaging/Shipping

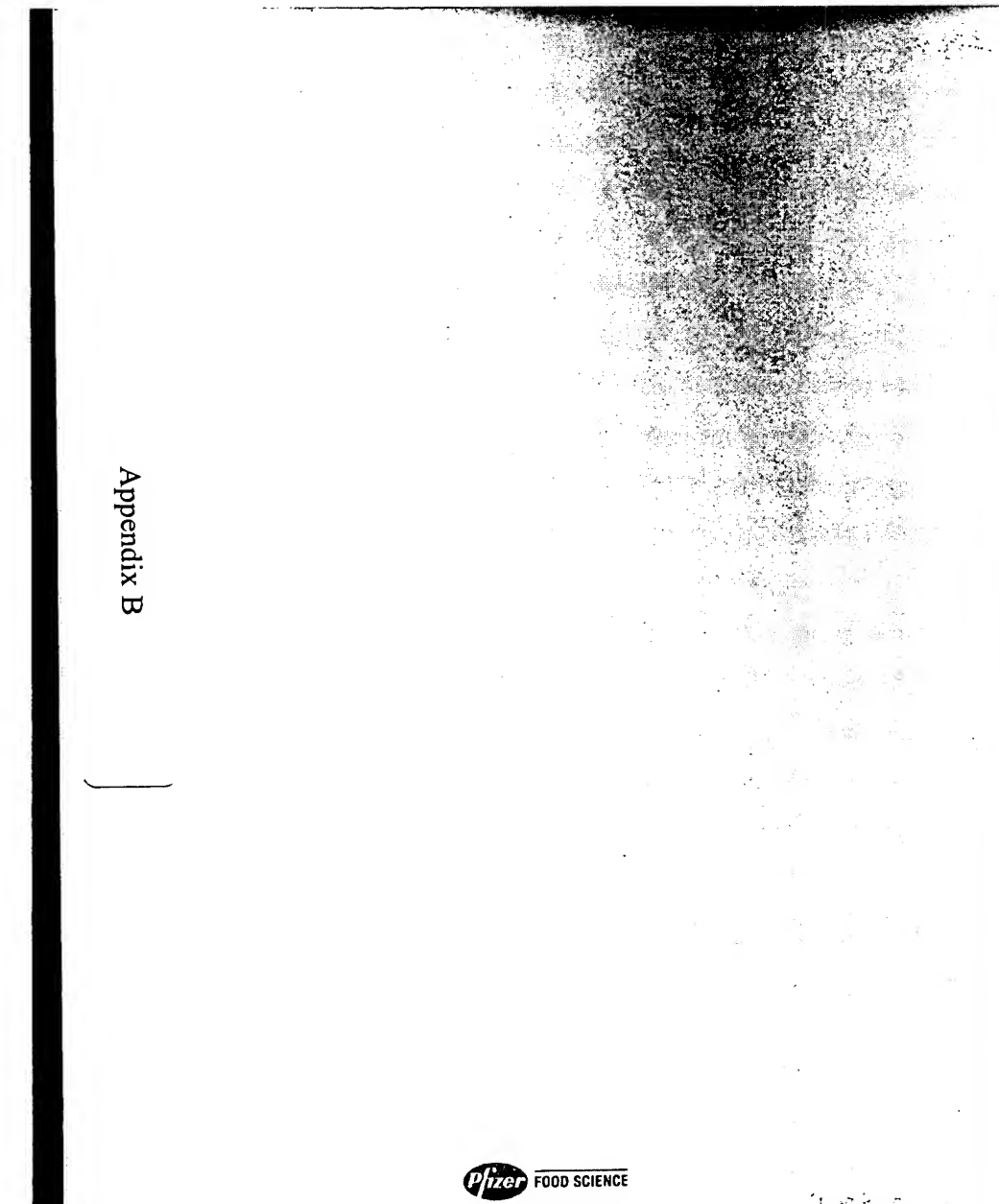
CAS Number 165450-17-9
U.S. Department of Transportation class, item, non-hazardous

The NutraSweet Company

neotame™

The NutraSweet Company
200 World Trade Center
Merchandise Mart Suite 936
Chicago, IL 60654
Phone: 800-323-5321 Fax: 312-873-5053
www.nutrasweet.com
www.neotame.com

Appendix B



Pfizer FOOD SCIENCE

PFIZER FOOD SCIENCE, DIVISION OF PFIZER PTY LIMITED. ACN 008 422 348. 38 WHARF ROAD, WEST RYDE, NSW 2114.
*TRADEMARK PFIZER INC. 6/95 S&H PFSAL0010

And

people who

DON'T.

Pfizer FOOD SCIENCE

ADDING SWEETNESS, NOT CALORIES.

For sweetening reduced and low-calorie foods and beverages, Aclame is the wise choice.

With a caloric content of just 1.4kcal per gram and high potency, very little of the product is used. At these small usage levels, Aclame, like other high potency sweeteners, has essentially no impact on the caloric content of foods. When used to sweeten in place of sugar it can help to substantially reduce calories.

HIGHLY STABLE, EVEN WHEN THE HEAT IS ON.

Aclame's unique structure assures excellent stability, effectively minimising potential problems with processing as well as extending shelf-life. Aclame's stability profile enables it to perform exceptionally well, even in foods that require high-temperature conditions such as baking.

Also, by offering superior stability across a broad range of pH levels and processing conditions, Aclame can be used in many different applications.

CONSIDER THE LIQUID ASSETS.

Aclame's excellent solubility in water and other polar solvents makes it an attractive sweetener to use in liquid products such as soft drinks and syrups, especially when the sweetener needs to be added in dry form.

Since Aclame has excellent hydrolytic stability, the quality and level of sweetness in a liquid system are maintained over time.

A LITTLE GOES A LONG WAY.

One of the most important properties in a sweetener is its potency.

Aclame is 2,000 to 3,000 times sweeter than sugar itself. Because this level of potency is so high, you'll use less Aclame to achieve the sweetness you desire. Utilising only a small amount of the product can simplify handling and processing techniques, making Aclame very easy to use.

A VERSATILE PERFORMER.

Aclame delivers superior sweetener performance in everything from confections and baked goods, to ice creams and beverages.

Since the sweetness profile of Aclame is so similar to sugar, Aclame is often used as the sole source of sweetness. However, in those instances when a unique sweetness is desired for a product, Aclame is completely compatible with other high intensity sweeteners.

With so much versatility to offer, Aclame will make it easier for you to develop the kinds of innovative foods today's sophisticated consumers are demanding.

ADD THE EXPERIENCE AND EXPERTISE OF PFIZER FOR COMPLETE SATISFACTION.

Pfizer has a thorough knowledge of food technologies.

We also have considerable product development expertise and resources, with a food technology laboratory in Sydney and access to resources in the United States.

Pfizer also has an excellent portfolio of other high-performance ingredients. These include:

- Litesse®, a one-calorie-per-gram bulking agent which helps maintain the bulking attributes of sugar in sugar-free foods.
- Dairy-Lo®, an all natural milk protein which provides creamy texture and mouthfeel in reduced fat foods.
- Veltol®, a flavour enhancer that helps round out and balance flavour profiles.

OUR KNOWLEDGE AND RESOURCES ARE AT YOUR DISPOSAL.

If desired, we can use our extensive knowledge and resources to help you develop new low-joule foods.

When you put it all together, there's only one conclusion: Life just got sweeter.

Potency.

A little goes a *long* way.

Aclame has a level of sweetness that is approximately 2,000 to 3,000 times greater than sucrose at typical usage levels. It depends upon the application and the desired sucrose equivalency.

Compared to other sweeteners in the marketplace, Aclame has a level of sweetness potency that is significantly greater.

Maximum Sweetness Potency in Water

	Potency Frequently Reported	Sucrose Potency at 2%	Sucrose Potency at 8%	Sucrose Potency at 10%
Sucrose	1.0	1.0	1.0	1.0
Acesulfame-K	200	204	77	34
Aclame	**2000**	**4500**	**2355**	**1640**
Aspartame	200	250	143	107
Na Cyclamate	30	26	27	18
Na Saccharin	300	510	188	0
Sucralose	600	614	520	385

Aclame's sweetness potency greatly exceeds that of other sweeteners.

Suggested Usage Levels of Aclame.

A single kilogram of Aclame provides the sweetening potency of between 2 metric tons and 3 metric tons of sugar. Typically, usage levels for Aclame range from 20 to 200ppm.

Alitame is a crystalline, non-hygroscopic dipeptide-based sweetener with a unique structure that enables high levels of sweetness and stability.

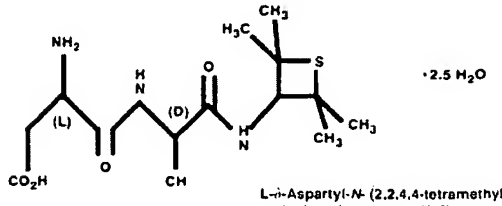
Aclame Suggested Usage Levels

Application	Use Level (ppm)		Sucrose Matched	Application	Use Level (ppm)		Sucrose Matched
Soft drinks:				Flavoured yoghurt	20	30	8-10%
Lemonade	40	45	10%	Custard	10	15	5.0%
Raspberry	45	50	11%	**Baked Goods:**			
Orange	45	50	12%	Muffin	80	100	15.5%
Cordial:				Cake	120	150	29.5%
Fruit	30	35	9%	**Other:**			
Nu-fruit	35	40	9.5%	Tabletop tablets	1 x 4 gram sachet		
Dairy:				Tinned fruit (pineapple)	80	90	15.8%
Ice Cream	50	70	18%	Jelly	55	65	13%
Flavoured milks	10	15	4%	Caramel bites	180	220	52%
Fruit Yoghurt (made up)	20	30	7.5%	Chocolate topping	50	70	42%

Due to its high sweetness levels, Aclame can be used in small quantities to achieve desired sweetness.

It is a member of the L-∂-Aspartyl-D-alanine amide series discovered by Pfizer Food Science in which the alanine carboxyl group is terminated as an amide of a novel amine (2,2,4,4-tetramethylthietanyl amine).

Alitame Structure.



L-α-Aspartyl-*N*- (2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide hydrate (2:5)
$C_{14}H_{25}N_3O_4S \cdot 2.5\ H_2O$
mw 376.5
CAS Registry Number: 99016-42-9

Alitame is a crystalline, non-hygroscopic powder – its unique structure enables high levels of sweetness and stability.

Pfizer FOOD SCIENCE

ACLAME™
Life Just Got Sweeter

Solubility.

Consider the *liquid* assets.

Due to Aclame's excellent solubility in most polar solvents, the sweetness of the product can be added as a solution or neat material.

ACLAME SOLUBILITY.

Solvent	Solubility (%W/V), 25°C
Water	13.1 (isoelectric pH 5.6)
Methanol	41.9
Ethanol	61.0
Propylene glycol	>40
Chloroform	0.02
n-Heptane	0.001

Due to its outstanding solubility, Aclame is easy to process in solution and can be used in an extensive range of foods.

Aclame can be added to the food system from a stock solution or as the dry material dissolved in available liquids from the formulation.

At Aclame's isoelectric point of pH 5.6, it is 13.1% soluble in water (w/v) at 25°C. Aclame is equally soluble in most liquid systems encountered in food applications.

The exceptional stablility of Aclame in solution, even at high temperatures, facilitates usage and processing of the product—making Aclame a very versatile sweetener for many different kinds of foods such as low calorie beverages and syrups.

Pfizer FOOD SCIENCE

ACLAME™
Life Just Got Sweeter

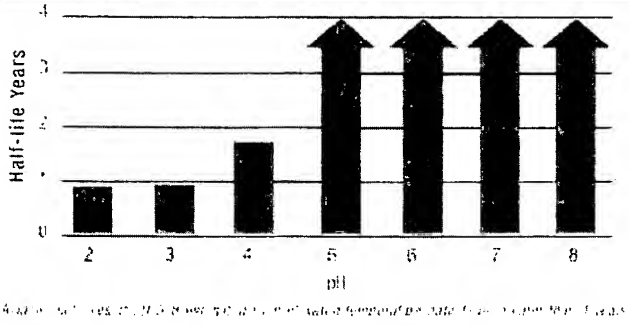
Stability.

Highly stable, *even* when the HEAT is on.

The unique structure of Aclame allows the product to deliver maximum stability across a wide range of pH levels and under many different food processing conditions.

This effectively reduces the potential for processing conflicts, while also increasing ease of use and extension of shelf life.

Stability of Aclame in Buffer Solutions at 23°C



Aclame offers excellent stability over a wide pH range, including lower pH aqueous systems.

Aclame is also very stable in aqueous environments. This provides the opportunity to use Aclame in a greater variety of foods including pasteurized processed and high temperature processed neutral pH food systems as well as confectionery and baked goods.

Additionally, Aclame offers excellent stability in lower pH aqueous systems.

At elevated temperatures, Aclame solutions of varying pH levels show good hydrolytic stability. Thus, Aclame provides thermal stability when thermal processing is warranted.

Elevated Temperature Stability of Aclame

100° C	13.5*	13.4	12.8
115° C	2.1*	2.1	2.1

*Half-life in hours

Concentrated Aclame solutions provide excellent stability when held at elevated temperatures.

These high levels of stability give food technologists extensive versatility in developing foods that will meet the diversified needs of today's consumers.

Pfizer FOOD SCIENCE

ACLAME™
Life Just Got Sweeter

Taste.

Adding *sweetness*, not calories.

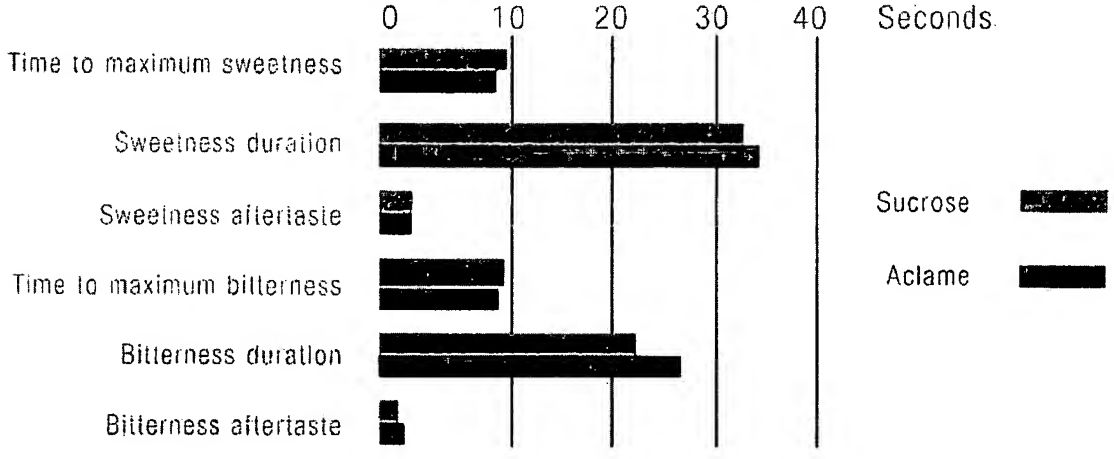
Sensory analysis indicates that Aclame's sweetness profile is similar to that of sugar. As a result of its unique composition, the product delivers a clean sweetness closely resembling the actual sweetness of sugar. When tested in water versus a 10% sucrose equivalent, Aclame performed exceedingly well, providing a very high level of sweetness potency.

The product's outstanding performance characteristics give it excellent versatility, allowing Aclame to be used alone or blended with other sweeteners to create the flavour profile and sweetness adaptations that are right for you.

Aclame has a caloric content of just 1.4 kcal (5.85 joules) per gram. And because of the product's exceptional potency, only small amounts are necessary to achieve desired sweetness.

Thus, while Aclame itself has essentially no impact on the caloric content of foods, when used as a replacement for sugar it can significantly reduce calories.

SWEETNESS AND BITTERNESS IN WATER AT 10% SUCROSE EQUIVALENCY.



Aclame has a sweetness and flavour profile similar to sugar.

Pfizer FOOD SCIENCE

ACLAME™
Life Just Got Sweeter

ACLAME MAXIMUM STABILITY.

Maximum Stability in Various Applications

Product	Process	Conditions	Aclame
Water, unbuffered	HTST	pH 3-5.4	~97%
Water, buffered	Batch Pasteurization	pH 3.7	~98%
Tablets	Lactose Carrier	23°C and 37°C x 2 years	Avg. 91%
Granulated Blends	Maltodextrin Carrier	23°C and 37°C x 2 years	Avg. 88%
3% Solution	Water Carrier	23°C and 30°C x 2 years	~91%
Yellow Cake	Conventional Baking	350°F x 35 min	~75%
Cookies	Conventional Baking	375°F x 9 min	~75%
Frozen Yogurt	HTST	180°F x 30 sec.	95%
Sugar Free Hard Candy	Batch Depositing	Addition with flavour and acid	85%
Lemon-Lime Soda	Conventional Process	23°C x 1 year and 30°C x 25 weeks pH 2.8	>70%

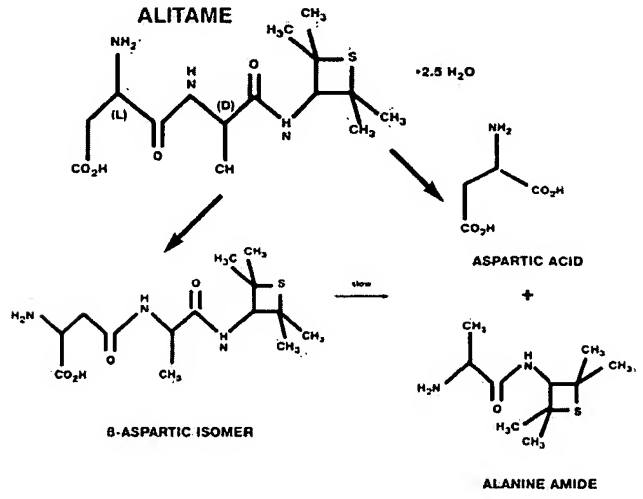
High levels of stability ensure that Aclame is adaptable to a wide variety of food processing applications.

Although Aclame has good stability some hydrolysis and isomerization can occur.

The major pathway involves hydrolysis of the aspartylalanine dipeptide bond to give aspartic acid and alanyl- 2,2,4,4-tetramethylthietane amide ("alanine amide"). The aspartic rearrangement common to all peptides bearing terminal aspartic acid, also occurs to give the aspartic isomer of Aclame.

This rearranged dipeptide hydrolyzes at a slower rate than Aclame to give the same product as those arising from the parent compound. No cyclization to diketopiperazine or hydrolysis of the alanine amide bond is detectable in solutions of Aclame that have undergone up to 90% hydrolysis. All three major products of hydrolysis and isomerization are completely tasteless at levels that are possible in foods.

ACLAME HYDROLYSIS AND ISOMERIZATION.



A minimal amount of hydrolysis and isomerization may occur in Aclame when used in some applications. However, this has no impact on taste.

Pfizer FOOD SCIENCE

ACLAME™
Life Just Got Sweeter

Neotame: The Next-Generation Sweetener

A new sweetener derived from aspartame that is [illegible] than sugar and does not have the undesirable [illegible] to some high-intensity sweeteners.

Indra Prakash, Glenn Corliss, Rao Ponakala, and Glen Ishikawa

Neotame, a new high-intensity sweetener and flavor enhancer, is expected to receive Food and Drug Administration approval for use in foods and beverages in the United States soon. Since it will then be the newest approved sweetener in the U.S., it is appropriate to review its development, characteristics, and potential uses.

Overview

Neotame is a derivative of the dipeptide composed of the amino acids aspartic acid and phenylalanine. It is 7,000–13,000 times as sweet as sugar and 30–60 times as sweet as aspartame. It is manufactured by The NutraSweet Co., Mt. Prospect, Ill., the company that developed the noncaloric sweetener aspartame.

It provides zero calories and has a clean, sweet, sugar-like taste with no undesirable taste characteristics. It is functional in a wide array of beverages and foods and can be used alone or blended with other high-intensity or carbohydrate sweeteners. It is stable under dry conditions, and has comparable stability to aspartame in aqueous food systems and more stable in neutral pH conditions (e.g., baking and yogurt).

The results of numerous safety studies confirm that it is safe for use by the general population, including children, pregnant women, and people with diabetes. In addition, since the product is not metabolized to phenylalanine, no special labeling for individuals with phenylketonuria (PKU) is required. Neotame has been approved for general use as a sweetener and flavor enhancer in Australia and New Zealand and is being reviewed in the U.S. and other countries.

Discovery and Manufacture

Neotame was the result of a long-term research program by The NutraSweet Co. to discover new high-intensity sweeteners with desirable taste characteristics. Working with The NutraSweet Co., French scientists Claude Nofre and Jean-Marie Tinti prepared a series of compounds by substituting the terminal nitrogen of aspartame with a number of hydrophobic groups and determined their sweetness compared to a 2% solution of sucrose. Aspartame substituted with a 3,3-dimethylbutyl group was the sweetest of the compounds tested and was selected as development product and called neotame (Nofre and Tinti, 1996b, 2000). This compound has the chemical structure as shown in Fig. 1.

As shown in Fig. 2, neotame can be made in one step by the reaction of aspartame with 3,3-dimethylbutyraldehyde in methanol, using hydrogen and a catalyst (palladium or platinum) under mild conditions (Nofre and Tinti, 1996a; Prakash, 1998). Other possible methods of preparation are from aspartame precursors via the reductive alkylation with 3,3-dimethylbutyraldehyde; peptide coupling of the L-aspartic acid derivatives and L-phenylalanine methyl ester; aminolysis of substituted oxazolidinone derivatives (Prakash, 2001; Prakash and Chapeau, 2000; Prakash et al., 2001b).

The authors are, respectively, Director of Organic Chemistry, Senior Food Scientist, Senior Food Scientist, and Director of R&D, The NutraSweet Co., 699 Wheeling Rd., Mt. Prospect, IL 60056. Authors Corliss, Ponakala, and Ishikawa are Professional Members of IFT. Send reprint requests to author Prakash.

Appendix C

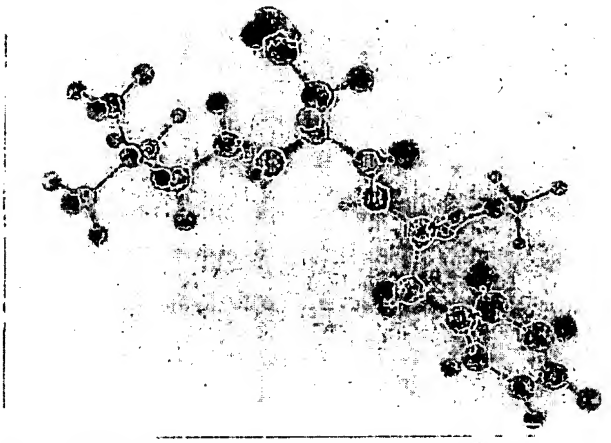


Fig. 1—3-dimensional structure of the neotame molecule

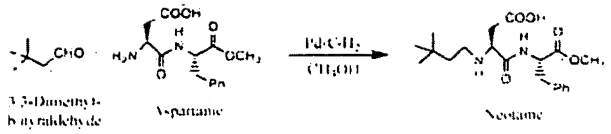


Fig 2—Manufacture of neotame by reaction of aspartame with 3,3-dimethylbutyraldehyde

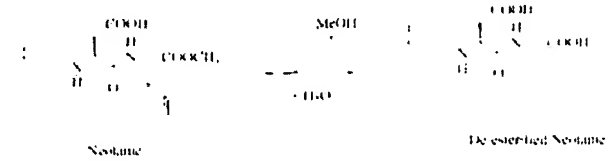


Fig 3—Major pathway of degradation of neotame under hydrolytic conditions

Characteristics

Neotame's physical, chemical, and sensory characteristics make it attractive for use as a sweetener in foods and beverages.

• **Chemical Characteristics.** Neotame is N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester (CAS registry No. 165450-17-9; proposed INS No. 961). It is a derivative of a dipeptide composed of the amino acids aspartic acid and phenylalanine. It contains both a carboxylic acid and a secondary amino group, with pK_a values of 3.03 and 8.08, respectively. It is capable of forming both acidic and basic salts, as well as complexes with various metals, thus affording unique delivery forms having improved solubility and other characteristics.

The two amino acids in neotame, aspartic acid and phenylalanine, are in the natural L-configuration. The other three possible isomers, L,D-, D,D-, and D,L-, lack the sweet taste of neotame (Prakash et al., 1999).

• **Physical Characteristics.** Neotame is a fairly low-melting hydrate (80.9–83.4°C). It is a white to off-white crystalline powder with 4.5% water of hydration, the empirical formula $C_{20}H_{30}N_2O_5 \cdot H_2O$, and a molecular weight of 396.48.

Its solubility in water is similar to that of aspartame (12.6 g/L vs 10 g/L at 25°C), but it is more readily soluble than aspartame in some solvents, such as ethanol, typically used in food systems and pharmaceuticals. Its solubility in water and ethyl acetate increases with increasing temperature. Using neotame in a salt form (e.g., as a phosphate salt) significantly increases the rate of dissolution.

• **Stability.** The stability of neotame is dependent on pH, moisture, and temperature. As a dry powder, it is stable for at least five years under proper storage conditions. In aqueous systems, pH stability follows a bell-shaped curve at a given temperature. The optimum pH for maximum stability is about 4.5. As expected, stability decreases with increasing temperature. Stability can be enhanced by the addition of divalent or trivalent cations in edible compounds (Schroeder and Wang, 2001b).

In aqueous systems (pH 2–8), the major decomposition pathway of neotame is through the hydrolysis of the methyl ester to form de-esterified or de-methylated neotame—N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine (Fig. 3)—which is also the major metabolite of neotame in humans. De-esterified neotame is not sweet.

Under conditions of use, neotame, unlike aspartame, does not degrade to phenylalanine. Also unlike aspartame, neotame does not form a diketopiperazine (DKP) derivative. Neotame is compatible with reducing sugars and aldehyde or ketone-based flavoring agents.

• **Sweetness.** Sucrose is the sweetness standard against which other compounds are compared. A compound with a "sucrose equivalence" of x% SE is equivalent in sweetness to an x% solution of sucrose in water. Neotame is approximately 8,000 times as sweet as sucrose and more potent than the high-intensity sweeteners currently marketed in the U.S.—aspartame and acesulfame K (200 times as sweet as sucrose), saccharin (300 times), and sucralose (600 times). It is a derivative of aspartame and is 30–60 times sweeter than aspartame. Its actual sweetness potency is dependent on the concentration required in various food or beverage products.

Because of its remarkable sweetness potency, neotame can be used in food and beverage products at considerably lower concentrations than other high-intensity sweeteners. In fact, consumer exposure to neotame will be much lower than exposure to flavoring ingredients such as vanillin, cinnamon, and menthol commonly used in foods and beverages.

The concentration–response curve for neotame (Fig. 4) was established using a trained sensory panel to evaluate the sweet-

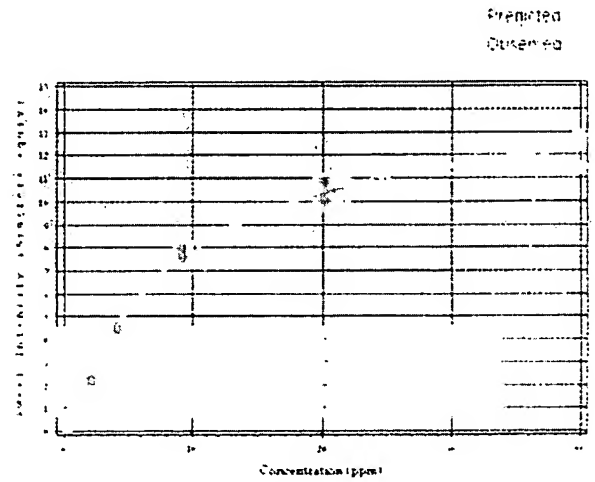


Fig 4—Sweetness intensity vs concentration of neotame in water

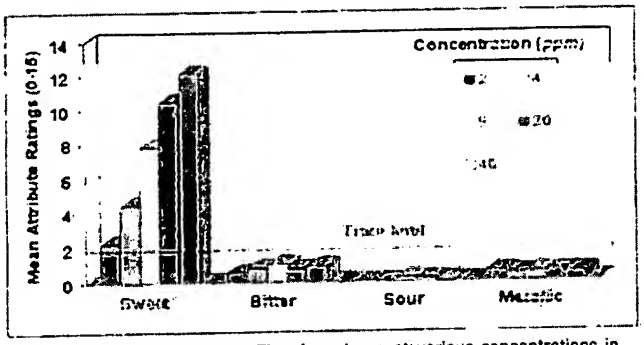


Fig. 5—**Descriptive taste profile of neotame** at various concentrations in water

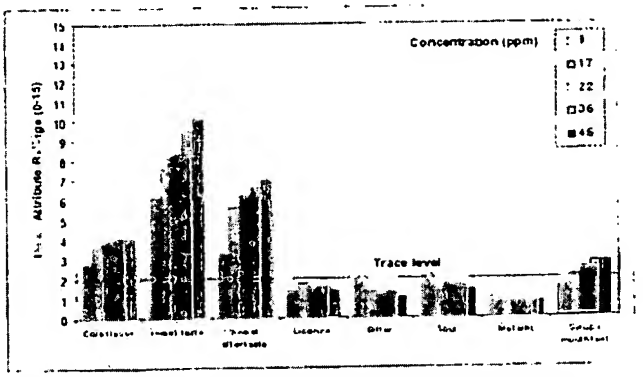


Fig. 6—**Taste profile of neotame** at various concentrations in a cola-flavored carbonated beverage

ness intensity of five solutions of neotame at increasing concentrations. Based on these data, neotame can reach an extrapolated maximum sweetness intensity (plateau) of 15.1% SE in water. Sweeteners such as aspartame, acesulfame K, sodium cyclamate, and sodium saccharin attain their maximum sweetness intensity in water at approximately 16.0, 11.6, 11.3, and 9.0% SE, respectively. In a cola formulation, neotame reaches a maximum sweetness intensity of 13.4% SE (DuBois et al., 1991).

• **Taste Profile.** A trained descriptive panel evaluated neotame and sucrose at comparable sweetness levels in water. Neotame's taste profile is very similar to that of sucrose, with the predominant sensory characteristic being a very clean, sweet taste. The sweetness increases as the concentration in water increases, but other taste attributes such as bitterness, sourness, and metallic taste are insignificant (Fig. 5). In a similar study with neotame in a cola drink, increasing the sweetener concentration from 9 to 46 ppm improved the desirable flavor attributes (cola flavor, sweet taste, and mouthfeel) but did not increase the undesirable notes (Fig.6).

• **Sweetness Temporal Profile.** The temporal profile of sweeteners demonstrates the changes in the perception of sweetness over time. This property is a key to the functionality of a sweetener and is complementary to its taste profile. Every sweetener exhibits a characteristic onset or response time and an extinction time. Most high-intensity sweeteners, in contrast to sugar, display a prolonged extinction time referred to as "linger."

As shown in Fig. 7, the sweetness temporal profile of neotame in water is close to that of aspartame, with a slightly slower onset and slightly longer linger. A longer sweetness linger can be beneficial in some products, such as chewing gum, where prolonged sweetness is a desirable quality.

The sweetness temporal profile of neotame may also be modified by the addition of hydrophobic organic acids, such as cinnamic acid, and certain amino acids, such as serine and tyrosine (Bishay et al., 2000b; Gerlat et al., 2000; Prakash et al, 2001a). Taste modifiers may be used in concentrations necessary to achieve the desired taste profile of a product for a desired application.

• **Synergy.** Blending of sweeteners is well known to improve taste characteristics and stability and provide sweetness synergy (Lavia and Hill, 1972; Schiffman et al., 1995; Scott, 1971; Verdi and Hood, 1993; Walters, 1993). A blend of neotame and saccharin provides 14–24% greater sweetness than would be predicted by adding together the sweetness intensities of the individual sweeteners (Pajor and Gibes, 2000). Such synergistic blends offer cost savings by decreasing the total amount of

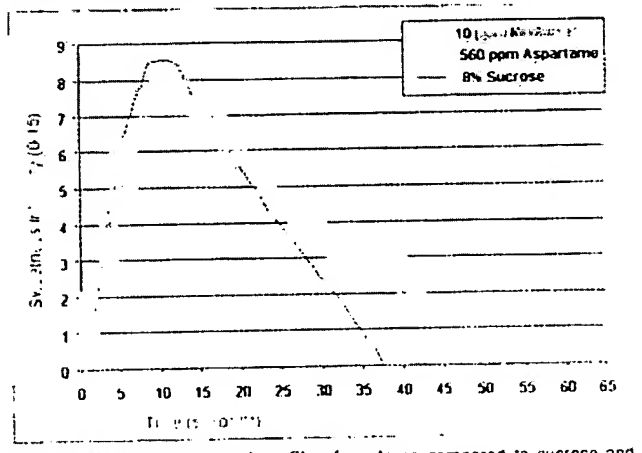


Fig. 7—**Sweetness temporal profile of neotame** compared to sucrose and aspartame at isosweet concentrations in water

sweetener needed. Neotame can be blended with nutritive sweeteners as well as other high-intensity sweeteners such as aspartame, acesulfame salts, cyclamate, sucralose, saccharin, and others (Nofre and Tinti, 1996b). Furthermore, the clean sweetness of neotame permits its substitution for substantial amounts of carbohydrate sweeteners without altering the flavor of the product.

Because time–intensity profiles of the sweeteners acting synergistically are different from those of the individual sweeteners and may also be different from that of sucrose, blends can be selected that combine or emphasize properties of the different sweeteners. The sweetness of acesulfame K is generally perceived fairly quickly. It may, therefore, provide some impact sweetness, but it often fades fairly quickly. Therefore, acesulfame combines particularly well with sweeteners having a more lasting sweetness, such as aspartame or neotame.

• **Sugar Substitution.** Neotame's clean sweet taste allows the food technologist to substitute a portion of a carbohydrate sweetener with neotame while maintaining a taste that is indistinguishable from the 100% carbohydrate product. For example, studies have shown that 20% of the carbohydrate sweetener can be replaced with 2.1 ppm of neotame in a carbonated cola soft drink, and the taste is indistinguishable from the 100% carbohydrate–sweetened cola beverage (Fig. 8). Neotame's potency may offer an economic benefit and, because it has no calories, a positive caloric benefit.

• **Flavor Modification and Enhancement.** Neotame can also be used to modify or enhance a product's flavor—the

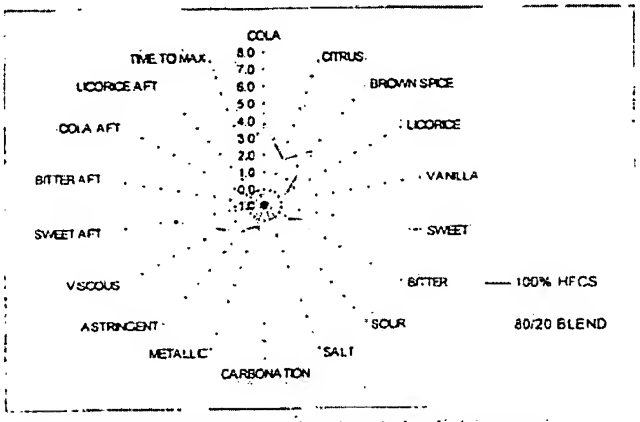


Fig. 8—Descriptive test results of carbonated cola beverages sweetened with 100% high-fructose corn syrup and a 20%/80% blend of HFCS and neotame

combined perception of taste, smell, and aroma. Products containing vitamins, nutraceuticals, pharmaceuticals, salt substitutes, and soy in various applications are often either bitter or harsh in flavor. The addition of neotame at a subsweetening level modifies or masks undesirable notes/qualities such as bitterness, astringency, and burning or cooling sensations. Undesirable attributes, such as the potential bitterness of caffeine, cocoa, and potassium chloride and the harsh notes of medicinals and plant extracts, can be modified or masked.

Neotame also reduces the bitter taste of potassium chloride in salt substitutes, thereby providing a cleaner salty taste. It reduces or eliminates "beany" flavor notes in soy products. And it modifies or enhances the attributes of many flavoring chemicals, including essential oils, oleoresins, plant extracts, reaction flavors, and mixtures thereof (Gerlat et al., 2000).

Food Applications

Historically, the stability and functionality of a new sweetener or an ingredient was determined for each food product before the sweetener was approved. This process generated redundant data. This redundancy could be avoided if products with similar ingredients and processing conditions could be reduced to representative test products for evaluation.

The functionality of neotame was demonstrated with a three-dimensional food matrix model representing the intended conditions of use in foods (Pariza et al., 1998). Based on experience with aspartame and the structural similarities of neotame and aspartame, product moisture, process temperature, and product pH were considered to be the key factors responsible for neotame stability and were selected to represent the three dimensions of the matrix.

Test products were prepared according to standard formulas, then packaged appropriately, stored at temperature conditions of up to 25°C and 60% relative humidity, and evaluated for stability at appropriate intervals. Neotame concentrations were determined using validated high-performance liquid chromatography methods.

Functionality (sweetness) of the test products was determined using panels consisting of 35–50 persons. Samples were appropriately prepared, served, and evaluated on a scale ranging from 5 ("much too sweet") to 1 ("not at all sweet"). The samples were considered functional if no more than 75% of the panelists rated the sweetness as 2 ("not quite sweet enough") and 1.

• **Cola-Flavored Carbonated Soft Drink.** Neotame remained functional for at least 16 weeks, consistent with currently marketed low-calorie carbonated soft drinks (Gerlat et al., 1999).

• **Hot-Pack Lemon Tea.** Neotame remained functional for approximately 25 weeks.

• **Powdered Soft Drink.** At each evaluation, the sweetness of the reconstituted drink received a rating of "just about right," indicating that the product was stable and functional as a sweetener during 52 weeks of storage.

• **Tabletop Products.** Neotame was considered stable and functional in tabletop products for at least 156 weeks of storage (FAP, 1998; Towb et al., 2002).

• **Chewing Gum.** Encapsulation improved neotame stability. Double coating with modified starch and hydroxypropyl methylcellulose protected it from degradation during storage for 52 weeks (Roefer, 2002).

• **Dairy Products/Strawberry Yogurt.** At the end of a 6-week period, the typical shelf life of these products, about 98% of the initial neotame remained. Sensory results showed that neotame had excellent functionality in yogurt (FAP, 1998; Gaughan et al., 1999).

• **Yellow Cake.** Neotame was functional, with 82% of the amount added to the batter remaining after baking at 350°F. After storage at 25°C and 60% relative humidity for 5 days—which is longer than cakes baked from commercial mixes are held for optimum freshness—there was only a 4% loss of neotame. The combined losses of about 20% did not affect sweetener functionality (Chinn et al., 1999; FAP, 1998).

• **Other Products.** Functionality has also been demonstrated in cereals and cereal-based foods (Ponakala and Corliss, 2000), nutraceuticals (Ponakala et al., 2000a), pharmaceuticals (Ponakala, 2001), edible gels (Ponakala et al., 2000b), and confectionery products (Jarrett, 2001).

Table 1 presents some typical use levels of neotame in various foods and beverages. Since neotame is extremely sweet, the use levels are expressed as parts per million rather than percentages. The ranges provided are for neotame used either as a single sweetener or as a component in a sweetener blend.

Delivery Forms and Benefits

Neotame can be prepared in a wide variety of forms, including agglomerated (Fotos and Bishay, 2001), granulated (Dron, 2001), extruded and spheronized (Dron et al, 2000), encapsulated (Ponakala et al., 1999), co-crystallized with sugar (Fotos et al., 2001), acid salts (Prakash and Wachholder, 2001a), basic salts (Prakash and Wachholder, 2001b), sweetener salts (Prakash and Guo, 2000b), amorphous (Schroeder and Wang, 2001a), metal complexes (Prakash and Guo, 2000a), cyclodextrin complexes (Bishay et al., 2000a), and liquid (Schroeder et al, 2000). In certain uses, these delivery forms offer various advantages over neotame powder, such as ease of handling, non-dustiness, and improved solubility characteristics bringing greater flexibility to product developers.

Neotame provides several benefits as a sweetener and/or flavor enhancer in food and beverage systems. It is noncaloric; it requires no PKU labeling; it is not likely to react with aldehydes and consequently may be compatible with flavors containing aldehydes. Because of its high potency, the quantity required to sweeten a product is about 1/30 to 1/60 of the amount of aspartame required. It enhances the flavor of some ingredients, such as mint and suppresses the beany notes of

soy, in various food and beverage systems. It masks bitterness. It can complement the flavor of root beer beverages. In fruit-based juices, because of the increased mouthfeel it contributes, juice solids can be reduced. It has a sparing effect on the flavoring agent vanillin in puddings; on cocoa, dairy component, and vanillin in chocolate and cocoa-based products; on dairy and fruit components, such as citric acid, in yogurt; and on tomato flavor in barbeque sauces.

Safety and Regulatory Status

The results of extensive research done in animals and humans using amounts of neotame that far exceed expected consumption levels clearly confirm its safety for the general population, including children, pregnant women, and people with diabetes. Neotame is not mutagenic, teratogenic, or carcinogenic and has no effect on reproduction. In addition, no special labeling for phenylketonuric individuals is required. The major route of metabolism of neotame is de-esterification. Both neotame and de-esterified neotame have short plasma half-lives, with rapid and complete elimination (FAP, 1998, 1999).

The Food and Drug Administration is currently reviewing a food additive petition for approval of neotame for general use in food as a sweetener and flavor enhancer, and petitions for regulatory approval have been filed in a number of foreign countries. Australia and New Zealand have already approved use of neotame as a sweetener and flavor enhancer.

Neotame's unique properties will provide the food technologist with another tool to produce innovative new foods and beverages to meet consumers' demands for great-tasting foods without all the calories of sugar.

Table 1—Typical neotame concentrations in various products when used as a sweetener

Product	Typical concentration (ppm)
Carbonated soft drinks	2–50
Cola	17
Lemon-lime	14
Root beer	20
Flavored water	15
Still beverages	2–20
Fruit punch	15
Lemonade	10
Ready-to-drink tea	5
Powdered soft drink, as is	200–2,000
Lemon-flavored	16
Tabletop sweetener, as is	600–4,000
Lemon tea	12
Bakery products	6–130
Cookie	25
Yellow cake	35
Chocolate cake	125
Filling	25
Frosting	25
Dairy products	5–50
Yogurt	15
Ice cream	15
Other frozen desserts	5
Chewing gum	10–1,850
Confections	1–200
Hard candy	5–20
Cereals	10–500
Extruded	25
Frosting	30
Edible gels	10–100
Nutraceuticals	15–250
Pharmaceuticals	1–100
Liquid sweetener	10–10,000
Sweetener tablets	30–12,000

REFERENCES

Bishay, I., Fotos, J., Desai, N., Cleary, M., and Schroeder, S. 2000a. The use of cyclodextrin to stabilize N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester. PCT Int. Appl. Pat. WO 00/15049. 646 S

Bishay, I., Prakash, I., Desai, N., and Gelman, Y. 2000b. Modification of the taste and physicochemical properties of neotame using hydrophobic additives. PCT Int. Appl. Pat. WO 00/69282.

Cano, B., Sotos, S., Ponakala, S., Ziegler, J., Bakhoum, M., Jarrett, T., Rossomme, E., and Cortes, G. 1999. Use of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester in baked goods, frostings and bakery fillings. PCT Int. Appl. Pat. WO 99/30566.

Chen, A. 2001. Process for making granulated N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester. PCT Int. Appl. Pat. WO 01/60842.

Chen, A., Bishay, I., Fotos, J., and Thorne, M. 2000. Stabilization of neotame with and without excipients. PCT Int. Appl. Pat. WO 00/57725.

Dubois, G., Walters, D., Schiffman, S., Warwick, Z., Boom, B., Pecore, S., Cross, S., Cain, B., and Brands, L. 1991. Concentration-response relationships of sweeteners. Chpt. 20 in "Sweeteners: Discovery, Molecular Design, and Chemoreception," ed. D.E. Walters, F.T. Orthoefer, and G.E. DuBois, pp. 261–276. Am. Chem. Soc.: Washington, D.C.

FDA. 1998. Monsanto Co.: Filing a food additive petition. FAP 8A4580. Food and Drug Admin., Fed. Reg. 63, 6762.

FDA. 1999. Monsanto Co.: Filing a food additive petition. FAP 9A4643. Food and Drug Admin., Fed. Reg. 64, 6100.

Fotos, J. and Bishay, I. 2001. Process for preparing an N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester agglomerate. U.S. patent 6,190,15[illegible].

Fotos, J., Bishay, I., Prakash, I., Waechholder, K., and Desai, N. 2001. Co-crystallization of sugar and N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester. U.S. patent 6,214,402.

Vaughan, W., Gofft, F., Ziegler, J., Walters, G., Lopa, I., Carlos, [illegible]. 1998. Neotame sweetener for dairy products and dairy product substitutes. PCT Int. Appl. Pat. WO 98/30578.

Verlaan, P., Hatchwell, L., Walters, G., Muraglio, A., and Sawyer, R. 2000. The [illegible]-lyl-α-aspartyl-L-phenylalanine methyl ester as flavor modifier. US patent appl. 09/465,937.

Verlaan, P., Milovanovic, S., Ponakala, S., Ziegler, J., Sawyer, R., and Walters, [illegible]. Neotame-based sweeteners for beverages. PCT Int. Appl. Pat. WO 99/06[illegible].

Verlaan, P., Walters, G., Bishay, I., Prakash, I., Jarrett, T., Desai, N., Sawyer, R., and [illegible]

ter 24 weeks, the aspartame-only beverage became less sweet, exhibiting a more artificially sweet taste and aftertaste. In contrast, the sweetness of the 30/70 acesulfame K/aspartame beverage remained close to that of the sucrose control. This is because in the aspartame-only beverage 50% of the aspartame degraded during storage, but blending aspartame with acesulfame K minimized this effect.

Thus, blending acesulfame K with other high-intensity sweeteners results in a sweetness profile that closely resembles that of sucrose. In addition, the fact that using acesulfame K blends provide longer shelf life has major implications for manufacturers of carbonated beverages.

Customizing Sweetener Blends

The results of these studies showed that there are significant benefits to be gained from customizing sweetener blends when developing new beverages or reformulating existing beverages. The role of the sweetener has progressed beyond that of a "calorie-reducing agent" to an ingredient which can add real value in influencing and optimizing taste and stability as well as economics.

Sweet Choices: Sugar Replacements for Foods and Beverages

▶ *from page 34*

nized As Safe, claiming exemption from the premarket or food additive approval requirements. After evaluating the GRAS notification submitted for tagatose, FDA told the manufacturer that it does not object to the manufacturer's determination of GRAS and that tagatose may therfore be used in the U.S. food supply.

• **Trehalose** is a multifunctional sweetener found naturally in honey, mushrooms, lobster, shrimp and food produced using baker's and brewer's yeast. It is commercially made from starch by an enzymatic process. It is metabolized much like other disaccharides. Trehalose protects and preserves cell structure in foods and may aid in the freezing and thawing process of many food products by assisting in maintaining the desired texture. It is also heat stable. It may be used in beverages, purees and fillings, nutrition bars, surimi, dehydrated fruits and vegetables, and white chocolate for cookies or chips. Because it provides 4 kcal/g and is only half as sweet as sucrose, it is more likely to be used for cell preservation than for sweetness. FDA has issued a letter of no objection to the manufacturer's self-determination of GRAS status for trehalose.

A Multitude of Choices

As indicated above, there are many sweeteners from which to choose. Most sweetener suppliers are pleased to provide information on how to best use their products, and some provide model formulations and/or blends or customized products for specific applications.

The information in this article is based on chapters in the author's book, Alternative Sweeteners, *3rd ed., published in 2001 by Marcel Dekker, Inc., New York, N.Y.*

Neotame: The Next-Generation Sweetener

▶ *from page 40*

Pajor, L. and Gibes, K. 2000. N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester synergistic sweetener blends. U.S. patent 6,048,999.

Pariza, M., Ponakala, S., Gerlat, P., and Andress, S. 1998. Predicting the functionality of direct food additives. Food Technol. 52(11): 56-60.

Ponakala, S. 2001. Pharmaceutical compositions containing neotame. PCT intl. applic. WO 01/028590.

Ponakala, S. and Corliss, G. 2000. Cereals and cereal-based food sweetened with neotame. PCT intl. applic. WO 00/056175.

Ponakala, S., Ziegler, J., Patterson, K., Brahmbhatt, D., Lui, P., Corliss, G., Chaudhary, V., Towb, A., Bishay, I., and Ansay, A., R. 1999. N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester as a sweetener in chewing gum. U.S. patent applic. No. 09/465,402.

Ponakala, S., Walters, G., Gerlat, P., and Hatchwell, L. 2000a. Nutraceuticals having N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester. PCT intl. applic. WO 00/057726.

Ponakala, S., Walters, G., and Schroeder, S. 2000b. Manufacture of edible gels sweetened with neotame. PCT intl. applic. WO 00/056176.

Prakash, I. 1998. Method for preparing and purifying an N-alkylated aspartame derivative. U.S. patent 5,728,862.

Prakash, I. 2001. Synthesis of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester using oxazolidinone derivatives. PCT intl. applic. WO 01/90138.

Prakash, I. and Chapeau, M.-C. 2000. N-3,3-Dimethylbutyl-L-aspartic acid and esters thereof, the process of preparing the same, and the process for preparing N-(N-(3,3-dimethylbutyl)- L-α-aspartyl)-L-phenylalanine 1-methyl ester therefrom. U.S. patent 6,077,962.

Prakash, I., and Guo, Z., 2000a. Metal complexes of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester. U.S. patent 6,146,680.

Prakash, I., and Guo, Z., 2000b. Sweetener salts of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester. U.S. patent 6,129,942.

Prakash, I., and Wachholder, K. 2001a. Acid salts of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester. U.S. patent 6,180,156.

Prakash, I. and Wachholder, K. 2001b. Basic salts of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester. U.S. patent 6,291,004.

Prakash, I., Bishay, I., and Schroeder, S. 1999. Neotame: synthesis, stereochemistry and sweetness. Synthetic Commun. 29: 4461-4467.

Prakash, I., Bishay, I., Desai, N., and Walters, D. 2001a. Modifying the temporal profile of the high-potency sweetener neotame. J. Agric. Food Chem. 49: 786-78.

Prakash, I., Scaros, M., Orlowski, V., and Moore, C. 2001b. A method for the preparation of N-neohexyl-L-α-aspartyl-L-phenylalanine methyl ester from imidazolidin-4-one intermediates. PCT intl. applic. WO 01/87927.

Roefer, W. 2002. Unpublished data. Dept. of Analytical Chemistry, The NutraSweet Co., Mt. Prospect, Ill.

Schiffman, S., Booth, B., Carr, B., Losee, M., Sattely Miller, E., and Graham, B. 1995. Investigation of synergism in binary mixtures of sweeteners. Brain Research Bull. 38(2): 105-120.

Schroeder, S. and Wang, R. 2001a. Amorphous N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester. U.S. patent 6,331,646.

Schroeder, S. and Wang, R. 2001b. Stability enhancement of sweeteners using salts containing divalent or trivalent cations. PCT intl. applic. WO 01/70049.

Schroeder, S., Wang, R., Ponakala, S., and Choudhary, V. 2000. Method of preparing liquid compositions for delivery of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester in food and beverage systems. PCT intl applic. WO 02/05651

Scott, D. 1971. Saccharin-dipeptide sweetening compositions. British patent 1,256,995.

Towb, A., Dron, A., and Walters, G. 2002. Drying of neotame with co-agents. PCT intl applic. WO 02/05660.

Verdi, R.J. and Hood, L.L. 1993. Advantages of alternative sweetener blends. Food Technol. 47(6): 94-101.

Walters, E. 1993. High intensity sweetener blends. Food Prod. Design 3(6): 83-92.